

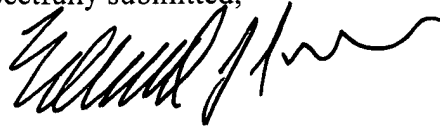
**REMARKS**

Applicant has amended page 1 on the specification to include a grant reference. A new page 1 showing the grant reference is enclosed.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



Edmund J. Sease, Reg. No. 24,741  
McKEE, VOORHEES & SEASE, P.L.C.  
801 Grand Avenue, Suite 3200  
Des Moines, Iowa 50309-2721  
Phone No. (515) 288-3667  
Fax No. (515) 288-1338  
**CUSTOMER NO: 22885**

Attorneys of Record

- rl -

Application No. 10/033,632

**AMENDMENT — VERSION WITH MARKINGS  
TO SHOW CHANGES MADE**

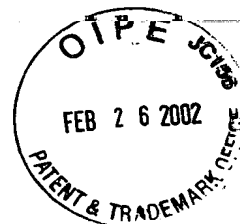
**In the Specification**

In the Specification, page 1, after the title insert  
the following:

**--GRANT REFERENCE**

This application was funded in part of the National  
Institute of Health under Grant No. GM55831.--

TITLE: DRUGS FOR SPINAL ANESTHESIA



GRANT REFERENCE

This application was funded in part of the National Institute of Health under Grant No. GM55831.

FIELD OF THE INVENTION

This invention relates to spinal anesthetics.

BACKGROUND OF THE INVENTION

Spinal anesthesia has obvious advantages. However, spinal anesthesia, using local anesthetics, is associated with acute side effects including hypotension and urinary retention, persistent sequelae like transient neurologic symptoms (TNS) and on occasion permanent deficits like cauda equina syndrome. Current research in spinal anesthesia has focused on the incidence of TNS and the dose and particular local anesthetic used, the effect of additives like epinephrine, and associated factors like patient position. There has been no recent progress in advancing new drugs for spinal anesthesia. This invention moves forward in the direction of new drugs for spinal anesthesia.

One alternative to conduction block for spinal anesthesia is blockade of synaptic transmission in the spinal cord. This could be accomplished by activation of inhibitory receptors or by antagonism of excitatory receptors. Glutamate is the major excitatory central nervous system neurotransmitter. Glutamate activates ionotropic excitatory amino acid (EAA) receptors that are highly prevalent in the nervous system and transmit information through both N-methyl-D-aspartate (NMDA) as well as nonNMDA EAA receptors. Ketamine, a drug used clinically in anesthesia, antagonizes NMDA receptors. Thus far, a clinical use for nonNMDA receptor antagonists, blocking alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainate receptors, has not been discovered. In experimental

kainate receptors, has not been discovered. In experimental animals, spinally administered non-NMDA receptor antagonists have been shown to inhibit nociception and produce motor dysfunction (Zahn PK, Umali E, Brennan TJ: Intrathecal non-NMDA excitatory amino acid receptor antagonists inhibit pain